Development of Transplantation Vasculopathy and Progression of Donor-Transmitted Atherosclerosis: Comparison by Serial Intravascular Ultrasound Imaging

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Background—Transplant coronary artery disease is a combination of atherosclerosis transmitted from the donor and new lesions of allograft vasculopathy. We sought to determine the morphological characteristics of allograft vasculopathy and differentiate it from donor-transmitted atherosclerosis with serial intravascular ultrasound.

Methods and Results—Intravascular ultrasound examination was performed in 93 patients at 27.2±15.0 and 369.7±23.9 days after transplantation. The maximally and minimally diseased sites were selected in each segment as defined by Coronary Artery Surgery Study classification. For each matched site, maximal plaque thickness was measured. Lesions (maximum plaque thickness ≥0.5 mm) present at baseline examination were defined as donor lesions. On follow-up, lesions that developed at previously normal sites were defined as de novo lesions. The distribution and severity of donor and de novo lesions were similar in proximal, mid, and distal segments. The de novo lesions were less focal (43% vs 74%) and more circumferential (69% vs 45%) compared with the donor lesions, but there was significant morphological heterogeneity. Similar numbers of patients with and those without donor lesions developed de novo lesions. Moreover, progression of donor lesions was not associated with the presence or absence of de novo lesions.

Conclusions—Differentiation between early allograft vasculopathy from conventional atherosclerosis by distribution and morphology of lesions alone is difficult. Serial intravascular ultrasound imaging with early baseline examination is necessary to make this distinction. This distinction is important because the progression of donor lesions and the development of de novo lesions are independent of each other. (Circulation. 1998;98:2672-2678.)

Key Words: coronary artery disease n transplantation n ultrasonics n lesion

Transplant coronary artery disease is the leading cause of late mortality, limiting the long-term success of heart transplantation.1–3 Coronary artery disease in heart transplantation recipients often is a combination of atherosclerosis transmitted from the donor and de novo lesions that develop after transplantation. The latter have been called “allograft vasculopathy or transplant arteriopathy.”4,5 The late stage of transplant coronary artery disease, as seen at necropsy, manifests as a severe diffuse obliterative process characterized by concentric intimal proliferation.6–8 However, the morphological characterization of early arteriopathy and its relation to donor lesions are not well defined.

Serial studies with intravascular ultrasound provide a unique opportunity to follow the natural history of the disease process.9 The sensitivity of intravascular ultrasound in identifying early changes in the transplanted heart is well documented.7,10–13 The measurements derived from intravascular ultrasound images have been validated with morphometric9,14 and angiographic15–17 measurements.

We sought to determine the morphology of early coronary lesions with serial intravascular ultrasound examinations. Our goal was to identify the lesions of allograft vasculopathy and differentiate them from atherosclerosis transmitted from the donor. We performed baseline intravascular ultrasound examination early after transplantation to identify donor lesions. One-year follow-up ultrasound examination was performed to identify the newly developed (de novo) lesions of transplant vasculopathy and to assess the changes in donor lesions.

Methods

Patient Population

The study group consisted of patients who underwent heart transplantation between December 1992 and October 1995. Patients who died during hospitalization, those who were not eligible for cardiac catheterization, and patients who did not give informed consent were excluded. The study protocol was approved by the hospital’s Institutional Review Board.
Intravascular Ultrasound Imaging

The baseline intravascular ultrasound examination was done within 2 months of transplantation. The repeat ultrasound imaging was performed at 1 year. Effort was made to image all 3 major epicardial vessels in all patients. Three arteries were imaged in 27 (29%) patients, 2 arteries were imaged in 38 (41%) patients, and only 1 vessel was imaged in 28 (30%) patients. Thus, 185 first-order epicardial vessels were examined in 93 patients. The right coronary artery was imaged in 48 (52%) patients, the left circumflex in 58 (62%) patients, and the left anterior descending in 79 (85%) patients.

The method of intravascular ultrasound imaging has been previously reported in detail. Briefly, a 30-MHz, 3.5F monorail ultrasound catheter (Boston Scientific) interfaced with a dedicated scanner (Hewlett-Packard) was passed over an angioplasty guide wire. The most distal transducer location was documented by cineangiography. Ultrasound images were recorded on S-VHS tape during a slow, distal-to-proximal manual pullback. Each vessel and its ultrasound landmarks (ie, branches, veins, pericardium) were identified during the pullback with the use of voice annotation. When needed, repeat imaging runs were performed and angiographic contrast injection was used to confirm the location of imaging sites, enabling precise matching of ultrasound images with angiographic segments. Before the 1-year examination, the cineangiograms and intravascular ultrasound images were reviewed by the operators to duplicate the imaging study.

Off-Line Intravascular Ultrasound Analysis

Baseline and follow-up ultrasound tapes were reviewed side by side on 2 identical video monitors in an intravascular ultrasound core laboratory. This simultaneous evaluation allowed accurate matching of pullback sequences. Cineangiographic as well as intravascular ultrasound landmarks such as side branches, pericardium, and cardiac veins were used in matching the sites. An operator digitized these full-motion ultrasound sequences (30 frames per second) on a 640x480 pixel matrix with 24 bits per pixel, using an image processing computer. Ultrasound images were considered suitable for analysis if images were free from ultrasound artifacts such as catheter angulation or nonuniform rotational distortion.

For each segment, defined according to Coronary Artery Surgery Study (CASS) classifications, all diseased sites at baseline examination were prospectively identified and included in the analysis. These sites were compared with the matching sites from the follow-up imaging. A different, retrospective methodology was used to capture the most severe de novo lesions of transplant vasculopathy. For this, from the 1-year examination, the normal or least diseased site and most diseased site from each segment were selected after excluding the sites with donor lesions. These sites were then identified from the baseline examination for measurement. In cases in which the entire segment was normal, 1 or 2 sites were selected from the segment. The operator examined the full-motion sequence before the selection of the single still frame to assist in optimal border delineation. The lumen and media-adventitial border of the selected still frames were manually traced, and direct measurements of cross-sectional area, circumference, minimum diameter, and maximum diameter were generated. Manual measurements of the minimum and maximum plaque thickness (Pmin and Pmax, respectively) were also performed.

The following definitions for lesion characteristics were used: (1) Focal: Focality describes the longitudinal extent of a lesion. The lesion was described as focal if there was at least 1 site in the same CASS segment that was completely normal. If the entire segment was involved by the disease process, the lesion was called diffuse. (2) Circumferential: Circumferentiality describes the axial distribution of a lesion. The lesion was circumferential if it involved the entire (>270 degrees of the arc) circumference of the vessel and noncircumferential if any arc of the vessel wall was free of disease (Figure 1). (3) Donor lesion: If Pmax was $0.5 \text{ mm at baseline}$ examination, it was defined as a donor lesion. (4) De novo lesion: If Pmax was $0.5 \text{ mm at follow-up}$, it was defined as a de novo lesion. (5) Progression of donor lesion: If the increase in maximal plaque thickness of a donor lesion on follow-up was $>0.5 \text{ mm}$, this term was used.

We have used Pmax for the definition of lesions and their progression because this is the most commonly reported parameter in the literature. However, plaque area ($P_{csa}$), calculated from lumen and external elastic membrane area measurement ($P_{csa} = \text{external elastic membrane area} - \text{lumen area}$), can serve as a reliable alternative to the Pmax measurement. Therefore, we sought a correlation of these 2 measurements in our data set. Pmax closely correlates with Pcsa measurement at baseline as well as at follow-up examination ($r = 0.88$, $P < 0.001$ for baseline and $r = 0.90$, $P < 0.001$ for follow-up examination). Furthermore, the progression in donor lesions and development of de novo lesions identified by the increase in Pmax was confirmed by the statistically significant increase in Pcsa.

Statistical Analysis

Normally distributed data are reported as mean±SD. The $x^2$ test or Fisher’s exact test was used to find significant differences between categorical variables. The unpaired 2-tailed $t$ test was used to compare mean values for continuous variables.

Results

Patient Characteristics

At our institution, 177 adult patients underwent heart transplantation between December 30, 1992, and October 30, 1995. Of these, 118 patients underwent cardiac catheterization early after transplantation. Hospital mortality, severe comorbid conditions, patient refusal, and scheduling constraints were reasons for not catheterizing the remaining 59 patients. At 1 year, 105 patients underwent catheterization. The causes of dropout were death ($n=11$) and technical considerations ($n=2$). Paired intravascular ultrasound data were available in 93 patients. Baseline and follow-up intravascular ultrasound examination were performed $27 \pm 15$ and $370 \pm 24$ days after transplantation,
TABLE 1. Recipient and Donor Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Recipient</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td>50.7 ± 10.8</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td></td>
<td>71/22</td>
</tr>
<tr>
<td>Triglycerides (pre), mg/dL</td>
<td></td>
<td>126.7 ± 73.1</td>
</tr>
<tr>
<td>Triglycerides (post), mg/dL</td>
<td></td>
<td>213.1 ± 123.9</td>
</tr>
<tr>
<td>LDL (pre), mg/dL</td>
<td></td>
<td>119.0 ± 40</td>
</tr>
<tr>
<td>LDL (post), mg/dL</td>
<td></td>
<td>158.8 ± 50.5</td>
</tr>
<tr>
<td>HDL (pre), mg/dL</td>
<td></td>
<td>32.0 ± 11.6</td>
</tr>
<tr>
<td>HDL (post), mg/dL</td>
<td></td>
<td>44.2 ± 14.1</td>
</tr>
<tr>
<td>Creatinine (pre), mg/dL</td>
<td></td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>Ischemic time, min</td>
<td></td>
<td>135.3 ± 47.0</td>
</tr>
<tr>
<td>Rejection (treated episodes), n</td>
<td></td>
<td>3.5 ± 2.9</td>
</tr>
<tr>
<td>Cause (DCM/ICM/other), n</td>
<td></td>
<td>31/47/14</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>13%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>Donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y*</td>
<td></td>
<td>29.8 ± 12.0</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td></td>
<td>64/29</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td>61%</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>13%</td>
</tr>
</tbody>
</table>

Pre indicates before transplantation; post, 1 year after transplantation; DCM, dilated cardiomyopathy; and ICM, ischemic cardiomyopathy.

Twenty-four (26%) donors were <30.0 years old and 5 (6%) were ≥50 years old.

respective. Donor and recipient characteristics are summarized in Table 1.

Morphology of Lesions

At baseline examination, 36 (39%) patients were identified with donor-transmitted atherosclerosis with involvement of 89 sites. These lesions involved proximal segments more frequently than mid and distal segments (Figure 2). The majority of the donor lesions were focal (74%), 55% were noncircumferential, and 57% of them involved a vessel bifurcation.

At follow-up imaging, 107 de novo lesions were identified in 42 (45%) patients. Similar to the donor-transmitted atherosclerosis, most of the de novo lesions were located in the proximal segments (Figure 2). Involvement of the bifurcation sites was also frequent (45%). Though the proportion of lesions in each distribution (proximal, mid, and distal) is comparable for donor and de novo lesions, more donor lesions are focal and noncircumferential compared with the de novo lesions (Table 2).

Severity of Lesions

The maximal plaque thickness of donor and de novo lesions in proximal, mid, and distal segments was similar (Figure 3). Moreover, there was no correlation between vessel area and plaque thickness (r=0.13, P=0.08). When the lesions involving different sites in the same coronary artery (n=45) were analyzed, plaque thickness of the more proximal lesions was similar to that of the distal lesions (proximal=0.97 ± 0.37 mm, distal=0.88 ± 0.26 mm; P=0.14). This was also the case for donor and de novo lesions (inset of Figure 3).

Progression of Donor Lesions

Donor lesion progression was noted at 23 sites in 15 (42%) of 36 patients. Progression was seen in 22% of proximal, 38% of mid, and 20% of distal segments (P=0.7). Ten (15%) lesions that were focal at baseline became diffuse on follow-up. Only 4 (8%) of the noncircumferential lesions at baseline progressed to involve the entire circumference of the coronary artery. However, the increase in plaque thickness of donor lesions was significantly less than that for the de novo lesions in the first year after transplantation (Figure 4).

Progression of donor-transmitted atherosclerosis was independent of the de novo lesion development. Of the 15 patients with progression, 6 (40%) had de novo lesions, and of the 21 patients without progression, 10 (48%) had de novo lesions (P=0.74). The converse was also true. Development of allograft vasculopathy was independent of donor-transmitted atherosclerosis. In 36 patients with donor lesions, 20 patients developed de novo lesions and 16 did not (P=0.11).

Discussion

Our findings indicate that at 1 year after transplantation, it is difficult to distinguish the lesions of donor-transmitted atherosclerosis from transplant vasculopathy by their morphological characteristics and distribution. Though the lesions of transplant vasculopathy tend to be more diffuse and circumferential than the atherosclerosis transmitted from donor lesions, both types of lesions have predilection for proximal segments and bifurcation sites. Despite these similarities, the development of de novo lesions and progression of donor-transmitted atherosclerosis are independent of each other.

Our understanding of the morphological aspects of transplant coronary artery disease is primarily based on necropsy studies, and to a lesser extent, on angiographic studies. In general, postmortem studies showed that transplant coronary artery disease involves distal vessels more than proximal, in a diffuse manner. However, necropsy studies allow assessment at one time point, usually at a late phase of the disease. These studies do not provide any information about...
the evolution of the disease process. On the other hand, annual angiographic examinations allow serial data collection. However, the insensitivity of coronary angiography in detecting early atherosclerotic changes limits its usefulness in understanding the development of transplantation coronary artery disease. Most of the previous morphological studies with intravascular ultrasound to study transplant coronary artery disease were done without serial examinations. A serial study with intravascular ultrasound has been published to establish feasibility, but morphology of lesions was not the focus of interest. This is the first serial intravascular ultrasound study that evaluates the morphology and distribution of transplant coronary artery disease.

Our study was prospectively designed to investigate transplant coronary artery disease with an early baseline intravascular imaging followed by a 1-year imaging. This approach allowed us to define donor-transmitted atherosclerosis from transplant vasculopathy. Moreover, multisegment imaging was performed to maximize sampling and to minimize errors in detecting and characterizing patterns of transplant coronary artery disease. This is distinct from other studies in which investigators have concentrated on 1 or 2 proximal segments of a single vessel. Our study population is representative of the heart transplantation population in general. Although some transplantation recipients were excluded, 79% of the hospital survivors and 89% of those who had catheterization were imaged by ultrasound. The 89% of patients who had a baseline study also had follow-up examination at 1 year.

Our findings demonstrate that though the early de novo lesions are more likely to be diffuse and concentric, a significant number of these are focal and noncircumferential. Besides, the distribution of de novo lesions throughout the length of the coronary arteries and predilection for bifurcation sites are similar to the donor-transmitted atherosclerosis. Even the severity of the de novo lesions in the proximal, mid, and distal segments is comparable. Thus the lesions of allograft vasculopathy at 1 year are indistinguishable from conventional atherosclerosis. This finding underscores the importance of serial examination and highlights the difficulty in interpretation of studies with cross-sectional design. These findings also suggest a role of local rheological factors in the development and progression of transplant vasculopathy as in conventional atherosclerosis.

The importance of donor-transmitted atherosclerosis in the genesis and progression of transplant vasculopathy is not known. In a predominantly angiographic study, preexisting coronary artery disease was found to be associated with accelerated allograft coronary artery disease. This finding was valid for angiographically evident coronary artery disease but not for intravascular ultrasound--detected atherosclerosis. In this study, the progression of preexisting lesions was not differentiated

TABLE 2. Morphology of Lesions

<table>
<thead>
<tr>
<th>Distribution of Analyzed Sites</th>
<th>Donor Lesions (Baseline), n=89</th>
<th>De Novo Lesions (1 y), n=107</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prox, n=323</td>
<td>Mid, n=172</td>
</tr>
<tr>
<td>Circumferential lesions</td>
<td>32 (51%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Focal lesions</td>
<td>44 (70%)</td>
<td>17 (81%)</td>
</tr>
</tbody>
</table>

Percentage under each number represents proportion of lesions in each distribution (proximal, mid, or distal) exhibiting designated morphological pattern (circumferential or focal). Donor lesions were statistically significantly more focal ($P=0.0009$) and more noncircumferential ($P=0.005$) than de novo lesions.

Figure 3. Distribution of lesions as divided into donor and de novo. As shown, donor lesions involved proximal, mid, and distal sites 20%, 12%, and 4%, respectively. Similarly, de novo lesions involved proximal, mid, and distal segments 20%, 18%, and 3%, respectively. Inset shows average mean lumen diameter [mean lumen diameter−(maximum lumen diameter−minimum lumen diameter)/2] of proximal, mid, and distal segments was 4.6±1.1 mm, 4.1±0.8 mm, and 3.8±0.7 mm, respectively.
from de novo lesions. Our observations demonstrate that atherosclerotic plaques in the transplanted heart does not predispose to allograft vasculopathy. It is also not known whether transplant vasculopathy leads to the progression of donor-transmitted atherosclerosis. We did not find any association between the progression of preexisting atherosclerosis and the development of allograft vasculopathy; however, the number of patients in each category is relatively small. Moreover, in the first year after transplantation, the rate of progression of donor lesions is slower than that of de novo lesions. Thus, despite many morphological similarities in the lesions of mild conventional atherosclerosis and early allograft vasculopathy, lack of interaction between the 2 disease processes and different rates of progression suggest the presence of independent biological determinants affecting their development and progression. However, there was predilection for the more proximal and bifurcation sites in both disease processes. These similarities in distribution can be explained by factors such as high shear forces that may contribute to the development of conventional atherosclerosis as well as transplant vasculopathy.

In this study, plaque thickness is defined as the distance from the intimal leading-edge to the external elastic membrane (adventitial leading edge). This is the standard method of measuring plaque thickness by intravascular ultrasound. The measurement of intima only (leading edge to trailing edge) requires delineating the internal elastic membrane, which can be difficult and imprecise. For all ultrasound techniques, the trailing edge location is often determined by ultrasound beam properties, not anatomic location. This latter method has been shown to be less accurate than the measurement technique that we used, which is based on delineating and tracing the external elastic membrane. The differences between definitions should be kept in mind while comparing the results of this study with other studies.

The threshold of plaque thickness (≥0.5 mm) used to define a lesion is based on the information provided by several histological and ultrasound studies. In a necropsy study, normal intimal thickness (not including media) averaged 0.21 mm (0.10 to 0.28 mm) in 21- to 25-year-old subjects, 0.22 mm (0.12 to 0.28 mm) in 26- to 30-year-old subjects, and 0.25 mm (0.18 to 0.35 mm) in 36- to 40-year-old subjects. Similarly, in a comparative ultrasound-histology study, patients with no known coronary artery disease, intimal thickness (without including media) was 0.24±0.11 mm. In this study, the medial thickness was 0.23±0.6 mm and did not vary significantly with intimal proliferation. Accordingly, the thickness of the normal intima and media in young and middle-aged humans ranges from 0.45 to 0.50 mm. Therefore, we have traditionally used the threshold of ≥0.5 mm to define a lesion. Clinical studies evaluating the risk factors for transplant vasculopathy commonly use this threshold.

Although the definitions used by us are rational and in accordance with most of the previous literature, we wanted to analyze the data by using a less stringent set of definitions to further validate our interpretations. Thus for addressing the concern that the use of the ≥0.5 mm threshold may underestimate donor atherosclerosis, we also analyzed our data using >0.3 mm threshold to define donor lesions. To exclude any influence of early donor progression of donor lesion.

**TABLE 3. Plaque Area of Donor and De Novo Lesions**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>n</th>
<th>Baseline (mm²)</th>
<th>1 Year (mm²)</th>
<th>Change (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor lesions: all</td>
<td>89</td>
<td>5.7±2.6</td>
<td>6.7±3.1</td>
<td>1.5±2.0</td>
</tr>
<tr>
<td>Donor lesions: progression</td>
<td>23</td>
<td>4.9±1.7</td>
<td>8.0±3.1</td>
<td>3.2±2.3</td>
</tr>
<tr>
<td>De novo lesions: all</td>
<td>107</td>
<td>1.7±1.4</td>
<td>5.6±2.0</td>
<td>3.9±2.0</td>
</tr>
<tr>
<td>De novo lesions with progression</td>
<td>26</td>
<td>2.3±1.5</td>
<td>5.0±1.3</td>
<td>2.7±1.5*</td>
</tr>
<tr>
<td>De novo lesions with progression</td>
<td>20</td>
<td>2.2±1.5</td>
<td>5.7±2.2</td>
<td>3.5±1.6*</td>
</tr>
</tbody>
</table>

*Plaque area of de novo lesions in patients with those without progression of donor lesions was not statistically significantly different (P=0.1).
atherosclerosis on development of transplant vasculopathy, de novo lesions were defined as lesions with baseline plaque thickness <0.15 mm and follow-up plaque thickness >0.3 mm. To capture even the minimal progression, we used a difference of >0.15 mm to define donor lesion progression. Using these definitions, the severity, distribution, and morphological aspects of the lesions were similar to the original analysis. The lack of interaction between the de novo lesions and donor disease was also evident in this analysis. However, with the use of the 0.3 mm threshold, the prevalence of donor-transmitted atherosclerosis was higher than previously reported.5,31,38

The differences between definitions and methodology should also be kept in mind when comparing our findings with previous studies in the literature. In histological studies, intramural arteries and arterioles are referred to as distal vessels. Angiography can identify distal vessels as small as 0.5 to 1.0 mm in diameter. We have defined the distal vessel according to CASS classification. Thus the distal vessels in this study do not represent very-small-caliber arteries and in this respect are not comparable with histological studies. Further, while interpreting the focality of a lesion, it should be recognized that the exact length of a lesion was not analyzed in this study because manual pullback was used for imaging.

This serial study points to the pitfalls of the morphological observations made at a single point in time with cross-sectional design and demonstrates that by morphological analysis it is impossible to distinguish donor-transmitted atherosclerosis from allograft arteriopathy. This finding underscores the role of serial intravascular ultrasound examination with early baseline study to make this distinction. It is meaningful to separate these two disease processes because they appear to behave independently despite their morphological similarities. In the future, to understand the pathophysiology of these diseases, it will be important to investigate potential clinical determinants separately for each disease process.

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Circulation. 1998;98:2672-2678
doi: 10.1161/01.CIR.98.24.2672

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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